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Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

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Background: **Delirium has recently been shown as a predictor of death, increased cost, and longer duration of stay in ventilated patients. Sedative and analgesic medications relieve anxiety and pain but may contribute to patients' transitioning into delirium.**

Methods: **In this cohort study, the authors designed *a priori* an investigation to determine whether sedative and analgesic medications independently increased the probability of daily transition to delirium. Markov regression modeling (adjusting for 11 covariates) was used in the evaluation of 198 mechanically ventilated patients to determine the probability of daily transition to delirium as a function of sedative and analgesic dose administration during the previous 24 h.**

Results: **Lorazepam was an independent risk factor for daily transition to delirium (odds ratio, 1.2 [95% confidence interval, 1.1–1.4]; $P = 0.003$), whereas fentanyl, morphine, and propofol were associated with higher but not statistically significant odds ratios. Increasing age and Acute Physiology and Chronic Health Evaluation II scores were also independent predictors of transitioning to delirium (multivariable P values < 0.05).**

Conclusions: **Lorazepam administration is an important and potentially modifiable risk factor for transitioning into delirium even after adjusting for relevant covariates.**

PATIENTS with severe sepsis and multiorgan dysfunction syndrome often have development of abnormalities in brain function manifested as delirium, coma, or both.[1–5] Delirium in intensive care unit (ICU) patients is a predictor of a threefold higher mortality over 6 months, higher cost of care, and significant ongoing cognitive impairment among survivors even after adjusting for severity of illness and other covariates.[4,6–9] These social and economic costs associated with delirium highlight the need for strategies to prevent delirium by identifying modifiable risk factors. Although numerous risk factors for delirium have been identified, data from previously published non-ICU cohorts do not necessarily apply to the ICU. For example, although previous studies have defined high-risk patients as those with three or more risk factors,[10,11] our group has shown that the average number of reported risk factors in ventilated patients was 11 ± 4 (mean ± SD),[7] which far exceeds the number for most non-ICU studies.

Although delirium may be a function of patients' specific underlying illness, it may also be due to iatrogenic and thus preventable causes. The exact mechanism of delirium is poorly understood, and its development and progression are thought to be related to imbalances in neurotransmitters from disease-related and management-related factors. Therefore, it remains challenging in cohort studies to quantify precisely the relative contribution of intrinsic *versus* iatrogenic risk factors. If there were data from rigorously designed ICU cohort studies that identified specific iatrogenic factors independently and temporally related to patients' transitioning into delirium, future randomized trials could then be designed.

There is published evidence suggesting that sedatives and analgesics, intended for increased patient comfort, may contribute to the development of delirium.[11–14] However, there are no prospective ICU studies addressing the temporal relation between time of administration of sedatives/analgesics and development of delirium, *i.e.*, it is difficult to ascertain from the literature whether sedatives and analgesics were administered to treat the delirium or whether the exposure to these agents resulted in delirium. We therefore undertook this investigation to test the hypothesis that sedative and analgesic medications are independent risk factors for the transition of patients into delirium after adjusting for relevant covariates such as age, sex, visual and hearing deficits, history of dementia, depression, severity of illness using modified Acute Physiology and Chronic Health Evaluation II (APACHE II) score, sepsis, history of neurologic disease (stroke, epilepsy, other central nervous system disorders), hematocrit (baseline), and daily serum glu-

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cose concentrations. We recognized that it was most appropriate to conduct the study using a statistical model that considered the temporal relation between drug administration and the outcome variable (*i.e.*, a time-dependent multivariable analysis).

Materials and Methods

Patients

The institutional review board at Vanderbilt University Medical Center, Nashville, Tennessee, approved this study, and informed consent was obtained from patients or their surrogate. Enrollment criteria included any adult, mechanically ventilated patient admitted to the medical or coronary ICUs at Vanderbilt University's 631-bed medical center from February 2000 to May 2001. Exclusion criteria included baseline neurologic diseases that would confound the evaluation of delirium as described previously.[14] A full description of the study protocol and clinical outcomes data from this cohort have been published previously.[8,9,14,15] The implication of sedatives and analgesics as risk factors for delirium in this cohort prompted us to conduct an in-depth analysis of the temporal relation between administration of these drugs and the transition of cognitive states. This investigation has not been previously published and is entirely original. At our institution, sedatives and analgesic medications were prescribed by physicians according to a protocol adapted from the guidelines of the Society of Critical Care Medicine.[16] The medications were titrated by the bedside nurses to achieve a target sedation level determined by the treating team by using the Richmond Agitation Sedation Scale (RASS)[15,17] and for pain by using the medical ICU's own behavioral pain indicator scale, similar to the behavioral pain scale of Payne *et al.*[18]

Statistical Analysis

Patients' baseline demographic and clinical variables were presented using means and SDs for continuous variables and proportions for categorical variables. Daily cognitive status was defined as normal, delirious, or comatose using well-validated and highly reliable instruments, the Confusion Assessment Method for the ICU (CAM-ICU)[8,19] and the RASS.[15,17] Normal was defined as RASS scores −3 and above and CAM-ICU negative. Delirium was defined as an acute change or fluctuation in mental status accompanied by inattention and either disorganized thinking or an altered level of consciousness (RASS scores −3 and above and CAM-ICU positive). Coma was defined as a RASS score of −4 or −5 where the CAM-ICU could not be assessed. The aim of the analysis was to estimate the probability of a transition to delirium as a function of sedative and analgesic drug administration in the previous 24 h and predetermined clinically relevant covariates. The most useful transition models are Markov chains for which the probability to transit from previous state to next depends on the previous observations.[20] Here, we used the first-order Markov chain model, which considers the following 6 (3 by 2) transitions: from normal, delirium, or comatose at previous 24 h to either normal or delirium status. These transition probabilities were estimated within a regression framework called "Markov regression" *i.e.*, a model that included as a covariate the patients' cognitive status measured 24 h previously. The Generalized Estimation Equation[21] was used to account for correlation among within patient observations. The explanatory variables used in the Markov model for analysis of analgesics (morphine/fentanyl) and sedatives (lorazepam/propofol/midazolam) were the $\log_e$ of total dose of each medication given during the 24 h before the assessment of the response variable. Therefore, the odds ratios (ORs) indicate percentage increase in odds of having delirium (*vs.* normal) event for every 1 $\log_e$ increase (micrograms for fentanyl and milligrams for the rest of the drugs) of dose of drug used in the previous 24 h. Covariates determined *a priori* after our review of the literature and organized focus group meetings with our ICU staff included age, sex, visual and hearing deficits, history of dementia, depression (measured with Geriatric Depression Scale short form[22]), severity of illness using modified APACHE II (removing the Glasgow Coma Scale), sepsis, history of neurologic disease, hematocrit (baseline) and daily serum glucose concentrations. To assess whether the effect of sedative drug on delirium was modified by the patient's cognitive status measured 24 h previously, a cross-product term of each sedative drug and the patient's cognitive status measured 24 h previously was added separately in the Markov regression model to preserve power for the analysis. To assess drug–drug interaction, we included a cross-product term between lorazepam and each of the other sedative and analgesic drugs (morphine, fentanyl, propofol, midazolam) into the Markov regression model.

Probability of transitioning to delirium was graphically presented using locally weighted scatter plot smoothing (LOWESS) method.[23] All data analyses were performed using SAS 8.02 (SAS Institute, Cary, NC) and R software version 2.1.0 (Free Software Foundation, Boston MA). A significance level of 0.05 was used for statistical inferences.

Results

Baseline Demographics

During the study period, we consecutively enrolled 275 adult mechanically ventilated ICU patients and monitored them daily for delirium and coma. Of those, 51 were excluded because of persistent coma, and another 26 were excluded because their lack of two consecutive cognitive assessments and thus no available data to determine a transition to delirium or coma. The baseline

Table 1. Baseline Characteristics of the Patients (n = 198)

Age, yr	55.5 ± 17.0
Men	103 (52)
Race	
White	155 (78)
Black	43 (22)
Charlson Comorbidity Index*	3.6 ± 2.8
Vision deficits	114 (58)
Hearing deficits	32 (16)
Blessed Dementia Rating Scale score†	0.2 ± 0.7
ADL score‡	0.9 ± 2.3
APACHE II score§	25.7 ± 8.4
SOFA score‖	10.0 ± 3.3
ICU admission diagnosis#	
Sepsis/acute respiratory distress syndrome	93 (47)
Pneumonia	37 (19)
Myocardial infarction/congestive failure	18 (10)
Chronic obstructive pulmonary disease	18 (10)
Gastrointestinal bleeding	18 (10)
Drug overdose	11 (6)
Hepatic or renal failure	9 (5)
Malignancy	5 (3)
Other	58 (29)

Data are presented as mean ± SD or n (%).

* Charlson Comorbidity Index (calculated using the Deyo method)[34,35] represents the sum of a weighted index that takes into account the number and seriousness of preexisting comorbidities. † Blessed Dementia Rating Scale[36] was validated as an instrument to be completed by surrogates to determine the presence of dementia. Scores range from 0 (best) to 17 (worst), with 4 or higher representing the most widely used threshold for dementia. ‡ Activities of Daily Living (ADL) scale[37] was completed by surrogates to estimate the baseline performance of the patient during the period just before the acute illness requiring admission to the intensive care unit (ICU). The authors used a modified Katz ADL scale that included 6 activities, scored from 0 to 2, for a range in total score of 0 (totally independent) to 12 (totally dependent). § Acute Physiology and Chronic Health Evaluation II (APACHE II)[38] is a severity of illness scoring system, and these data were calculated using the most abnormal parameters during the first 24 h after admission to the ICU. APACHE II scores range from 0 (best) to 71 (worst). ‖ Sequential Organ Failure Assessment (SOFA)[39,40] is an organ failure scoring system that was also calculated using the most abnormal parameters during the first 24 h after admission to the ICU. SOFA scores range from 0 (best) to 24 (worst). # The admission diagnoses were recorded by the patients' medical team as the diagnoses most representative of the reason for ICU admission. Patients were sometimes given more than one admission diagnosis by the medical team, resulting in a column total of more than 100%.

characteristics of the 198 patients composing our study population are presented in table 1. Patient's cognitive status was observed for a total of 1,071 days in the ICU. Of those, we excluded observations if data from a previous day was missing, because that would preclude our ability to determine a transition in cognitive status. A total of 696 observations from the 198 patients were included in the analysis.

Multivariable Analysis and Markov Modeling of Sedatives and Analgesics

Table 2 shows the results of using the Markov regression model to conduct multivariable analysis of sedative and analgesic medications as risk factors for transitioning to delirium. After adjusting for covariates as described in Materials and Methods, lorazepam was an independent risk factor for daily transition to delirium (OR, 1.2; $P = 0.003$), although the other four medications were associated with trends toward significance (midazolam OR, 1.7; $P = 0.09$; fentanyl OR, 1.2; $P = 0.09$; morphine OR, 1.1; $P = 0.24$; propofol OR, 1.2; $P = 0.18$) (see table 2 footnote for further description). More detailed data on lorazepam are depicted in figure 1, which shows LOWESS estimation of the probability of transitioning to delirium by dose of lorazepam and indicates that the incremental risk is large at low doses and plateaus at higher doses. The plateau in the graph indicates that incremental exposure beyond 20 mg lorazepam in the preceding 24 h does not significantly increase the probability of transitioning to delirium, because at that dose the probability of the transition to delirium is 100%. We also assessed for drug–drug interaction between lorazepam and other drugs in a multivariable model. There

Table 2. Multivariable Analysis of Sedative and Analgesic Medications as Risk Factors for Transitioning to Delirium/Coma or Delirium Only*

Medication	Transitioning to Delirium Only Odds Ratio (95% CI)	*P* Value
Lorazepam	1.2 (1.1–1.4)	0.003
Midazolam	1.7 (0.9–3.2)	0.09
Fentanyl	1.2 (1.0–1.5)	0.09
Morphine	1.1 (0.9–1.2)	0.24
Propofol	1.2 (0.9–1.7)	0.18

* Odds ratios in this table can be interpreted as indicating the following: every unit dose of lorazepam (in $\log_e$ milligrams), administration in the previous 24 h was significantly associated with a 20% risk increase in the daily transition to delirium. Midazolam, morphine, and propofol were also measured in milligrams, whereas fentanyl was measured in micrograms. The odds ratios were adjusted for the following baseline variables: age, sex, visual and hearing deficits, history of dementia, depression, severity of illness using modified Acute Physiology and Chronic Health Evaluation II (removing the Glasgow Coma Scale component), sepsis, history of neurologic disease (stroke, epilepsy, other central nervous system), baseline hematocrit, daily glucose concentration, and cognitive status at previous 24 h, and the other medication listed. All drug variables were log-transformed for the analysis because of nonlinearity of data.

CI = confidence interval.

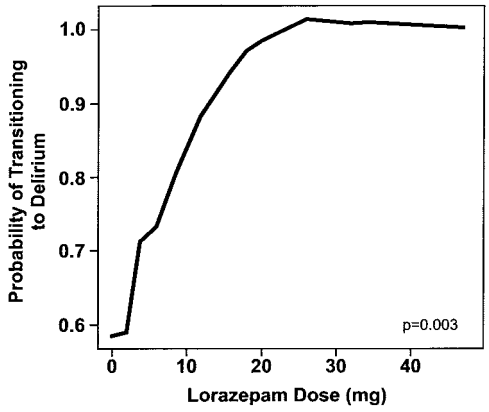

Fig. 1. Lorazepam and the probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at around 20 mg/day.

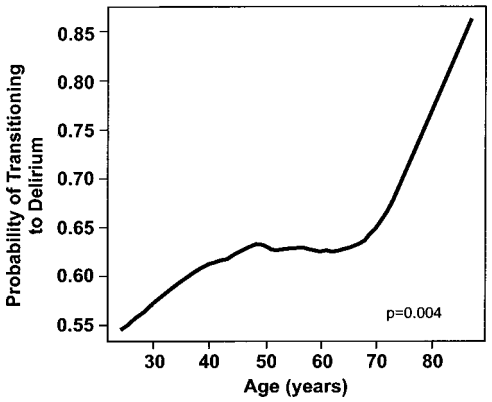

Fig. 2. Age and the probability of transitioning to delirium. The most notable finding related to age was that probability of transitioning to delirium increased dramatically for each year of life after 65 yr.

was no interaction detected in transitioning to delirium (all P values > 0.05), indicating that the combined use of the two drugs does not further increase the risk of transition to delirium. Interestingly, tests for interactions between lorazepam and previous cognitive status were also not significant, suggesting that previous cognitive status did not modify the contributory risk of these medications in transitioning into delirium.

Relation between Age and Severity of Illness versus *Transitions into Delirium*

Figure 2 shows LOWESS estimation of the probability of transitioning to delirium by age (years) and indicates that the incremental risk is large for those older than 65 yr. Figure 3 shows LOWESS estimation of the probability of transitioning to delirium by APACHE II severity of illness scores and indicates that the incremental risk becomes larger up to a score of 18 and then plateaus. The adjusted OR of transitioning to delirium for age was 1.02 (1.00–1.03; $P = 0.04$). This OR suggests that for each additional year, the probability of transitioning to delirium increased by 2%. Tests for interactions between age and delirium were negative. The adjusted OR of transitioning to delirium for APACHE II score was 1.06 (1.02–1.11; $P = 0.004$). This OR suggests that for each additional APACHE II score, the probability of transitioning to delirium increased by 6%. We also tested interaction by including a cross product term between lorazepam and age to assess if the effect of lorazepam was modified by age. Tests for interactions between lorazepam and age were negative.

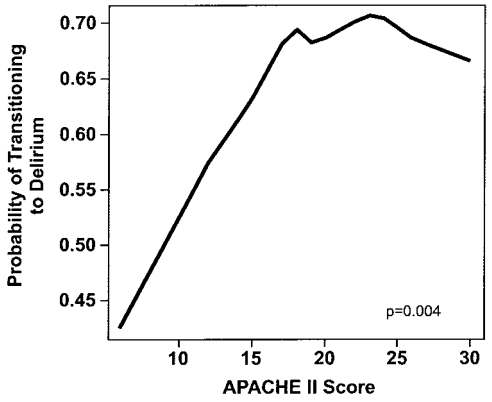

Fig. 3. Severity of illness and the probability of transitioning to delirium. The probability of transitioning to delirium increased dramatically for each additional point in Acute Physiology and Chronic Health Evaluation II (APACHE II) severity of illness score until reaching a plateau APACHE score of 18.

Antipsychotics and Anticholinergic Drug Exposure

Antipsychotic drugs were administered to 75 (38% of 198) patients; of those, 66 (88%) experienced delirium during their ICU admission. The administration of antipsychotics (*e.g.*, haloperidol or olanzapine) in these patients was not associated in univariate analysis ($P = 0.33$) or in multivariable analysis with transitions in status of delirium ($P = 0.39$). Anticholinergic drugs (*i.e.*, atropine, diphenhydramine, bupropion hydrochloride, metoclopramide, prochlorperazine, promethazine) were administered to 63 (32% of 198) patients, of whom 52 (83%) experienced delirium during their ICU stay. The administration of anticholinergics was not associated in univariate analysis ($P = 0.54$) or in multivariable analysis with delirium ($P = 0.82$).

Discussion

Sedative and analgesic medications are routinely administered to patients on mechanical ventilation, in accordance with widely recognized clinical practice guidelines,[16] to reduce pain and anxiety. The third component of the clinical practice algorithm published in these same guidelines is delirium. Of pain, anxiety, and delirium (three key components of the guideline's treatment algorithm), only delirium has been determined to be an independent predictor of mortality and ongoing morbidity such as long-term cognitive impairment. The chief findings of this study are that the very medication we give to reduce anxiety is independently associated with the development of delirium. Specifically, every unit dose of lorazepam was associated with a higher risk of transitioning into delirium during each subsequent 24-h period even after adjusting for 11 relevant covariates.

Similar associations between delirium and psychoactive medications have been published in postsurgical patients. Marcantonio *et al.*[11] performed a nested case–control study within a prospective cohort of postoperative patient patients who had development of delirium and found an association between benzodiazepines and meperidine use and the occurrence of delirium. Similarly, Dubois *et al.*[13] have shown that opiates (morphine and meperidine) administered either intravenously or epidurally may be associated with the development of

delirium in medical/surgical ICU patients. Studies such as these have generated concern regarding whether these drugs were actually responsible for the transition to delirium or were given as a result of delirium. Our study is the first to show the independent and temporal role of sedatives and analgesics in contributing to patients' transition to delirium.

Although it should be emphasized that these medications have an important role in patient comfort, healthcare professionals must also strive to achieve the right balance of sedative and analgesic administration through greater focus on reducing unnecessary or overzealous use. Instituting daily interruption of sedatives and analgesics or protocolizing their delivery have both been shown to improve patient outcomes.[24–26] Unfortunately, no studies to date have measured whether such techniques were accompanied by a lower prevalence of delirium. Based on the above-mentioned outcomes studies,[24–26] the Society of Critical Care Medicine's guidelines[16] recommend that ICU teams of physicians, nurses, and pharmacists set clinically appropriate target sedation levels using a well-validated sedation scale. Healthcare teams should routinely readdress these target levels each day to ensure titration of medications to the desired clinical endpoint.

Our findings indicate relevant differences between specific classes of medications. Benzodiazepines form the cornerstone of sedative regimens to relieve anxiety in the ICU,[16,27,28] although significant regional and international variations exist. Lorazepam was the most consistent and significant predictor of transitioning into delirium in our cohort. This is in light of the fact that it is identified as the "drug of choice" for treating delirium in critically ill patients in a recent text[29] and by 16% of respondents in a recent international survey.[30] Among opiates, fentanyl had higher and more significant ORs for transitions to delirium than morphine, although the number of patients who used morphine was considerably smaller. Although sedative and analgesic practices vary in ICUs around the world,[28] some physicians opt to use opiates for the "double effect" of analgesia and sedation, thereby reducing the need for benzodiazepines or propofol. In the context of the findings of our study and current guidelines that prioritize pain control, such an approach may be prudent.

As mentioned in the introduction, the pathophysiology of delirium is complex and poorly understood, and our lack of understanding extends to the mechanism or prognostic implications of delirium caused by the different psychoactive medications. Benzodiazepines and propofol have high affinity for the γ-aminobutyric acid receptor in the central nervous system.[31] This γ-aminobutyric acid mimetic effect can alter levels of numerous neurotransmitters believed to be deliriogenic. Novel sedative agents that are γ-aminobutyric acid receptor–sparing may help to reduce some of the cognitive dysfunction seen in ICU patients. The approval of α_2-receptor agonists such as dexmedetomidine for short-term sedation in the ICU[32] has stimulated research in this area. Recently, Maldonado *et al.*[33] showed in a prospective but unblinded randomized trial that cardiac surgery patients sedated intraoperatively at sternal closure with dexmedetomidine had a dramatically lower incidence of delirium postoperatively (8%) as compared with those sedated with propofol (50%) or midazolam (50%). These findings must be confirmed to determine whether differing sedation strategies translate into improved clinical outcomes.

Several limitations of this investigation warrant consideration. Our primary goal was to better understand the independent relation between sedatives and analgesics. To do this, our model incorporated numerous covariates that were deemed relevant *a priori*. However, this list was not all-inclusive. It is possible that other unmeasured covariates such as renal and hepatic dysfunction, hypoxemia, and sleep deprivation could have altered the results. Second, more frequent delirium assessments per day would have allowed an even better tracking of transitions in cognitive status and drug administration, but our methods are still much more rigorous than previously published non-ICU databases addressing this topic. Third, we used administered drug dose rather than plasma concentrations of the medications. There are few studies that have attempted to use *in vivo* drug concentrations, and it is not clear that such concentrations are superior to drug dose, because the choice of drug- and patient-specific metabolic parameters may influence the correlation between the drug and the cognitive outcome. Fourth, we excluded observations for which there were no accompanying assessments within a 24-h period. This and the fact that we did not have data on surgical ICU patients could limit the widespread generalizability of our findings. We could only get a cursory look at midazolam because of a small sample size. The infrequent use of midazolam represents the high adherence we had to the Society of Critical Care Medicine guidelines. Lastly, we were only able to conduct a cursory investigation into the role of anticholinergic medications, antipsychotics, and the interactions between the sedatives and analgesics as risk factors for transition to delirium. Although these were all not statistically significant, we did not have the power to make formal conclusions. Having a proper control population that received no sedation would have made the association between benzodiazepines and delirium much stronger. However, that would not be ethically appropriate in mechanically ventilated critically ill patients, where pain and anxiety must be addressed. Availability of newer agents that produce analgesia and anxiolysis may provide an ethical alternative to the current "standard of care" of sedative and analgesic regimens. In addition, studies comparing acute and chronic cognitive impair-

ment in patients receiving standard of care sedation *versus* protocolized target-based sedation with daily wake-up trials may provide a better understanding as to whether a reduction in the exposure to sedatives/analgesics improves neurologic outcomes. These limitations in our study represent excellent opportunities for future research efforts that may advance this field of study.

Conclusion

In this study, we used Markov regression modeling and documented that in addition to advancing age and APACHE II scores, there is an independent and dose-related temporal association between receiving lorazepam and transitioning to delirium, even after adjusting for relevant covariates. These data suggest that clinicians are faced daily with treatment choices that represent a double-edged sword for our patients. Considering that delirium is a predictor of death and other adverse outcomes, investigators should consider prospective interventional studies to determine whether differing management strategies or selection of sedative/analgesic agents are associated with reductions in delirium and other short- and long-term clinical outcomes.

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